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# Co-Catalyzed C(sp$^3$)−H Oxidative Coupling of Glycine and Peptide Derivatives

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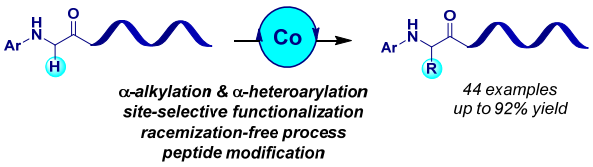
*Supporting Information Placeholder*

**ABSTRACT:** Cobalt-catalyzed selective α-alkylation and α-heteroarylation processes of α-amino esters and peptide derivatives are described. These cross-dehydrogenative reactions occur under mild reaction conditions and allow for the rapid assembly of structurally diverse α-amino carbonyl compounds. Unlike enolate chemistry, these methods are distinguished by their site-specificity, occur without racemization of the existing chiral centers and exhibit total selectivity for aryl glycine motifs over other amino acid units hence providing ample opportunities for peptide modifications.




Owing to the emergence of peptides and peptidomimetics at the forefront of pharmaceutical research and the limited availability of amino acids genetically encoded,[1] the development of new methodologies for the straightforward chemical modification of α-amino carbonyl compounds represents a challenging task of prime scientific interest.[2] Although most classical α-functionalization methods are hitherto limited to carbanion chemistry,[3] and solid phase techniques,[4] the last years have witnessed the upsurge of catalytic C−H functionalization approaches as atom-economic and environmentally friendly means for the direct modification of glycine and peptide derivatives.[5] Of particular importance are *Cross-Dehydrogenative Couplings* (CDCs) pioneered by Li which involve the dual oxidation of two distinct C−H bonds in a catalytic fashion.[6] These type of reactions are mostly catalyzed by copper and iron salts, and hence the implementation of alternative metal catalysts could open up new horizons in the realm of organic chemistry. In this respect, cobalt catalysis[7] has recently received a great deal of attention and provides new dogmas for achieving practical and unconventional bond-disconnections that were beyond reach using other metals. Despite the existence of various Co-catalyzed CDC reactions,[8] Co-catalyzed functionalization of amino esters and peptide derivatives remains virtually unexplored.

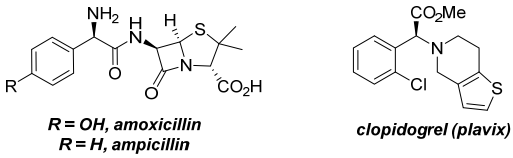
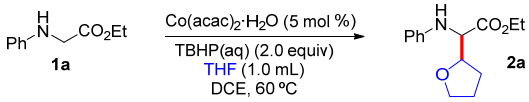



**Figure 1. Importance of aryl glycines in medicinal chemistry**

Aryl glycines are important nonproteogenic amino acids prevalent in a vast array of glycopeptide antibiotics and common key intermediates in the production of β-lactam antibiotics.[9] Some relevant examples are vancomycin, amoxicillin and ampicillin which contain aryl glycine residues (Figure 1). Conventional approaches for the preparation of aryl glycine compounds involve the Strecker synthesis,[10] the Petasis[11] and the Ugi reaction.[12] However, the direct functionalization of glycine or glycine-containing peptides through metal-catalyzed CDC processes clearly represents a practical, yet challenging, alternative.[13] Li and coworkers elegantly introduced efficient Cu-catalyzed α-functionalizations of glycine and peptide derivatives with a variety of highly reactive nucleophiles (boronic acids, alkynes and indoles).[13k-l] Despite the remarkable importance of the method, the success of the oxidative process was limited to the particular use of *p*-methoxyphenyl glycine amides and related α-amino esters were found unreactive. Herein we report on the development of an unprecedented Co-catalyzed site-selective alkylation and heteroarylation reaction with cyclic ethers and indoles, respectively. Our method features the use of a combination of cobalt salts as practical cost-efficient catalysts along with an aqueous solution of *tert*-butyl hydroperoxide as inexpensive oxidant. Remarkably, it represents a versatile synthetic tool of utmost importance for the assembly of a wide variety of substituted *N*-aryl α-amino esters and short peptides hence broadening the synthetic scope of existing methodologies to produce molecular diversity from inexpensive biomass in a selective and rapid manner.

**Table 1. Co-catalyzed C(sp$^3$)−H alkylation of 1a with THF[a]**

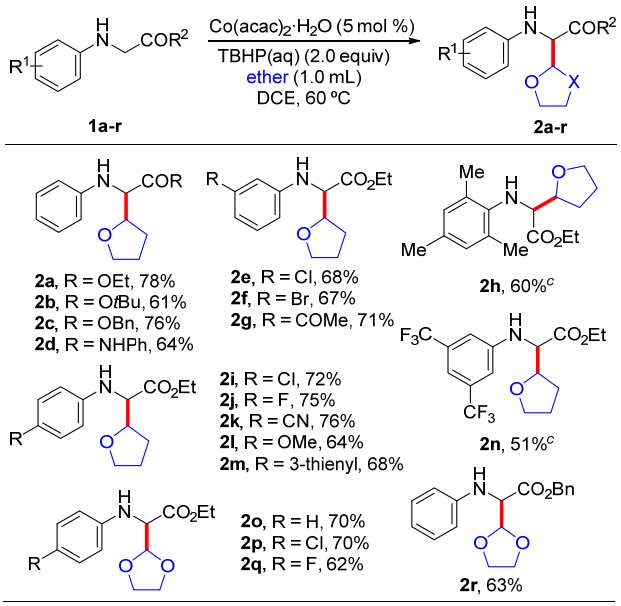



| entry | change from standard conditions | **2a** (%)[b] |
|---|---|---|
| 1 | none | 78 |
| 2 | without $Co(acac)_2·H_2O$ | 0 |
| 3 | without TBHP(aq) | 0 |
| 4 | TBHP(dec) instead of TBHP(aq) | 48 |
| 5 | without DCE | 61 |
| 6 | under air | 54 |
| 7 | $K_2S_2O_8$ instead of TBHP(aq) | 0 |
| 8 | DCP instead of TBHP(aq) | 0 |
| 9 | $Co(OAc)_2$ instead of $Co(acac)_2·H_2O$ | 69 |
| 10 | $Co(acac)_3$ instead of $Co(acac)_2·H_2O$ | 64 |
| 11 | $CoBr_2$ instead of $Co(acac)_2·H_2O$ | 77 |
| 12 | $CoCl_2$ instead of $Co(acac)_2·H_2O$ | 71 |

[a] Reaction conditions: **1a** (0.5 mmol), $Co(acac)_2·H_2O$ (5 mol %), TBHP(aq) (2.0 equiv), THF (1.0 mL), DCE (1.0 mL) at 60 ºC for 24 h under argon. [b] Yield of isolated product after column chromatography. TBHP (aq) = *t*BuOOH 70% in $H_2O$; TBHP (dec) = *t*BuOOH 5.0-6.0 M in decane; DCP = dicumyl peroxide.

Given the prevalence of ethers in a plethora of natural products and drugs together with their appealing use in CDC reactions,[14] we first analyzed the viability of using Co catalysis in the dehydrogenative alkylation of *N*-phenyl glycine ester (**1a**) with THF. After systematically evaluating the reaction parameters,[15] we found that a combination of $Co(acac)_2·H_2O$ (5 mol %) and an aqueous solution of TBHP in the presence of 1,2-dichoroethane as

**Scheme 1. Co-catalyzed C−H alkylation with cyclic ethers[a,b]**

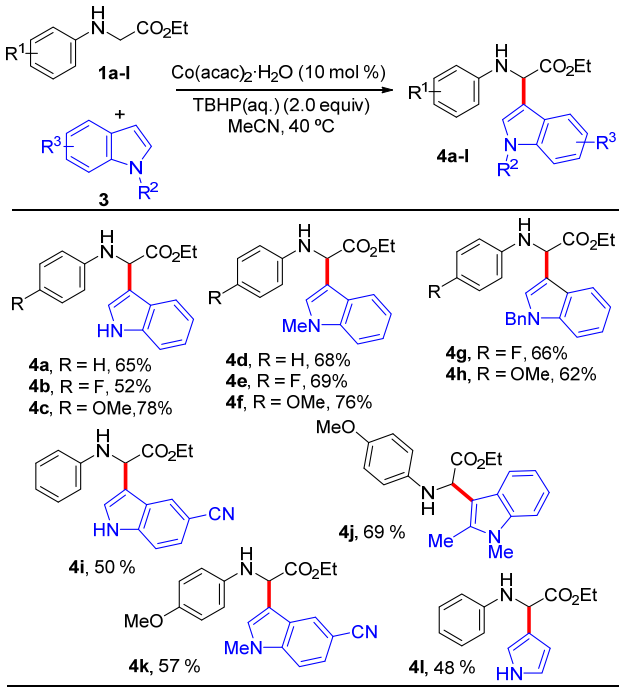



[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Reaction performed at 80 ºC.

solvent afforded α-alkylated glycinate **2a** in 78% yield (Table 1, entry 1). Control experiments revealed that all the reaction parameters were critical for success (entries 2-3). Importantly, an aqueous solution of TBHP was found superior than its analogue in decane (entry 4), which represents a practical bonus in terms of economics and sustainability; other related oxidants were shown unreactive (entries 7-8). A variety of metal sources were tested (entries 9-12), but the easy-to-handle and cheap $Co(acac)_2{\cdot}H_2O$ provided slightly better yields. Remarkably, a competitive double-oxidative dehydrogenative cyclization toward the formation of quinolone-fused lactones[16] was not observed, thus evidencing the significant subtleties of our Co-based catalytic system *vs* the use of other metals.

With optimal conditions in hand, we next examined the generality of our transformation by exploring a variety of *N*-aryl α-amino carbonyl compounds with ethers as feedstock substrates. Not only α-amino esters (**1a-c**) but also amides (**1d**) underwent the desired alkylation in good yields. As shown in Scheme 1, the process turned out to be widely applicable regardless of the nature of the aryl ring. Importantly, several functional groups were perfectly accommodated such as halides (**2e-f**, **2i-j**, **2n**, **2p-q**), ketones (**2g**), nitriles (**2k**), ethers (**2l**) and heterocycles (**2m**). Notably, even sterically demanding α-amino ester **1h** also smoothly underwent alkylation reaction. Of paramount significance is the use of 1,3-dioxolane as coupling partner due to the fact that its CDC would provide a masked formyl derivative upon a practical and aldehyde-free synthetic protocol. In this regard, the reaction turned out to be exclusively selective towards the C2 position providing **2o-r** as single regioisomers. We next envisioned the application of our Co-based method to the use of more powerful nucleophiles such as indoles. To our delight, after slight modification of the reaction conditions,[15] the use of cobalt catalysis allowed for the efficient coupling process of numerous α-amino esters **1a-l** and indole derivatives **3** under mild reaction conditions. As depicted on Scheme 2, *N*-methyl and *N*-benzyl indoles as well as versatile free-NH indoles underwent the target heteroarylation, regardless

**Scheme 2. Co-catalyzed C−H heteroarylation with indoles [a,b]**



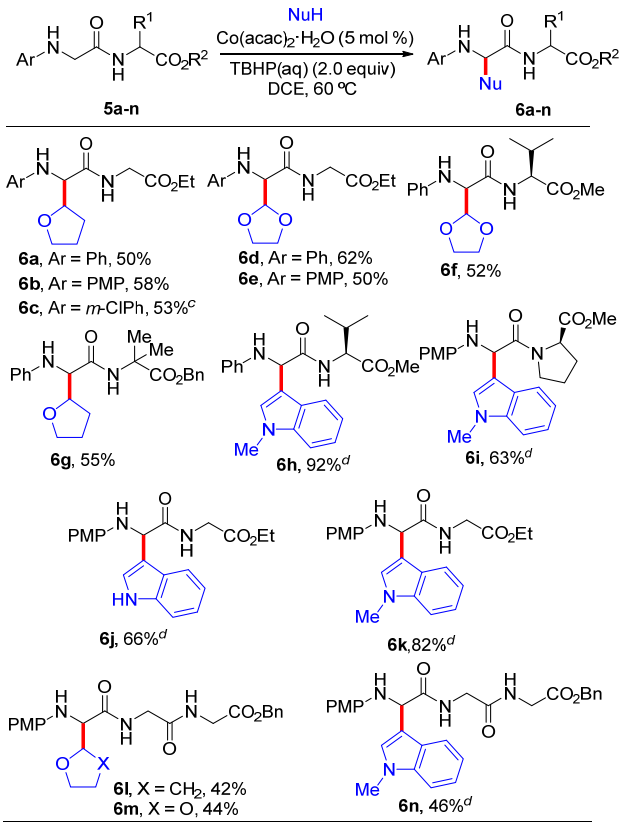

[a] Reaction conditions: **1a** (1.0 mmol), **3** (0.5 mmol), $Co(acac)_2{\cdot}H_2O$ (10 mol %), TBHP(aq) (2.0 equiv), MeCN (1.0 mL) at 40 ºC for 24 h under argon. [b] Yield of isolated product after column chromatography, average of at least two independent runs.

of the electronic nature of the *N*-aryl glycinate.[17] Notably, sterically hindered 2-substituted indole **3j** reacted to give the corresponding product **4j** in good yield. Besides, other heteroaromatic substrates such as less reactive simple pyrroles could be also utilized to produce heteroarylated glycinate **4l**, albeit in moderate yield. Noteworthy, the method was found tolerant with the presence of synthetically valuable functional groups such as nitriles (**4i**, **4k**).

Encouraged by these promising results, we decided to tackle the more challenging task of selectively functionalizing short peptides, which are typically prone to undergo oxidative cleavage[18] and hence difficult to manipulate. Importantly, simple dipeptides **5a-k** and tripeptides **5l-n** underwent the desired α-functionalization reaction both with ethers and indoles to furnish the corresponding products **6a-n** in moderate to excellent yields (Scheme 3). Whereas the heteroarylation event can be achieved upon copper catalysis[13k-l] or through aerobic auto-oxidative conditions,[16c] to the best of our knowledge our Co-catalyzed functionalization with cyclic ethers represents the first example of a highly selective alkylation of peptides featuring the use of feedstock substrates.[13d] In all cases, the *N*-aryl group directed the CDC to occur exclusively on the terminal Gly unit even in the presence of other Gly residues and not even traces of the functionalization of other residues were observed. Interestingly, dipeptides bearing valine and proline units also delivered the coupling products **6f**, **6h** and **6i**, respectively, in 52-92% yields. Remarkably, in the latter cases HLPC analysis verified the full preservation of the chiral integrity of the existing stereocenters.[15] Accordingly, our method scores over enolate chemistry which not only suffers from lack of regioselectivity in cases where the peptide contains multiple Gly residues, but also because of the often observed racemization due to the strong basic conditions required to deprotonate α-protons to the adjacent carbonyl moiety. Notably, unlike Cu-based system,[13k-l] the success of the process was not limited to the use of activated *N*-PMP-Gly-Gly-OEt but

also peptides bearing *N*-Ph (**6a**,**6d**,**6f-h**) and even *N*-*m*-chlorophenyl group (**6c**) provided the corresponding products in good yields. As a result, our Co-catalyzed approach outperforms known methods for the site-selective functionalization of small peptides.

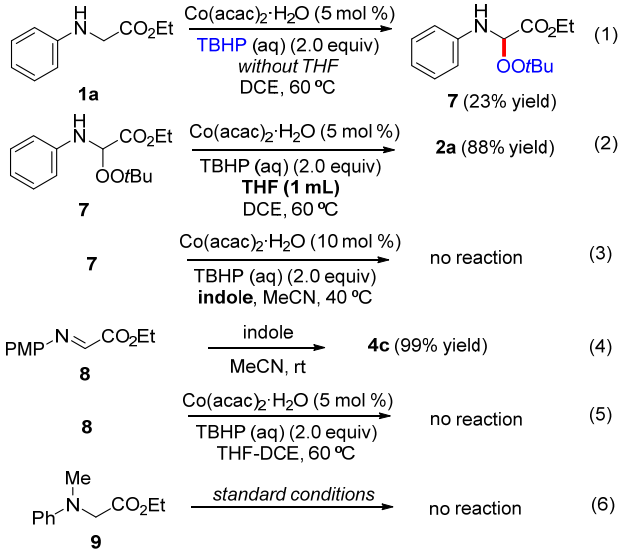
**Scheme 3. Co-catalyzed α-functionalization of peptides**[a,b]




[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Reaction performed at 80 °C. [d] Reaction conditions as for Scheme 2.

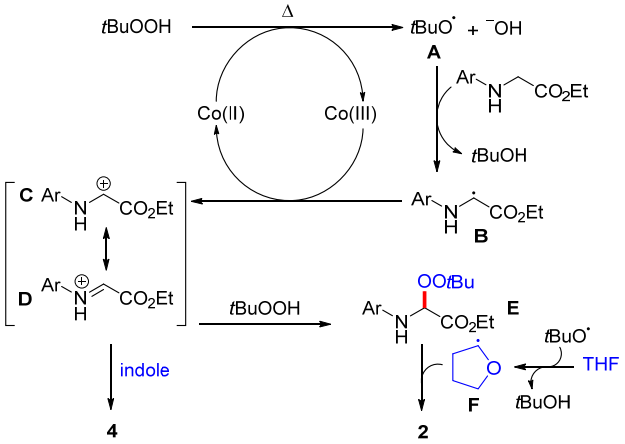
In order to gain some insights into the reaction mechanism, we carried out the following experiments. On one hand, we found that the CDC of amino ester **1a** with both indole and THF were entirely inhibited in the presence of radical traps such as TEMPO and BHT, which indicated that a radical mechanism may be operative. On the other hand, when glycinate **1a** was submitted to the coupling conditions in the absence of THF the α-*tert*-butyldioxyl intermediate **7** was isolated in 23% yield [Scheme 4, eq (1)]; the latter species was found to be stable and could be fully characterized by NMR spectroscopy.[19] Interestingly, peroxide derivative **7** provided the corresponding alkylated product **2a** in 88% yield under the optimized conditions [Scheme 4, eq (2)], thus evidencing its possible key role as a competent reaction intermediate within our catalytic cycle. Conversely, it did not react with indole [Scheme 4, eq (3)]. Curiously, whereas treatment of imine **8** with indole furnished the corresponding coupling product **4c** in 99% yield at room temperature in the absence of cobalt and oxidant [Scheme 4, eq (4)], such imine **8** remained unreactive under our oxidative alkylation conditions with THF [Scheme 4, eq (5)], thus revealing that a distinct mechanistic scenario could be operative in each case. Furthermore, our Co-catalyzed C−H functionalization processes upon tertiary amine **9** were unsuccessful [Scheme 4, eq (6)], which highlights the crucial role of the free-NH aryl group.

**Scheme 4. Control experiments**




On the basis of the above results and previous literature reports,[8,13] a plausible reaction mechanism is proposed in Scheme 5. The reaction would start with the Co(II)/Co(III)-induced decomposition of *t*BuOOH to produce *tert*-butoxy radical **A**.[20] Subsequently, the corresponding aryl glycine would undergo Hydrogen Atom Transfer (HAT) by radical species **A** to furnish alkyl radical intermediate **B**, which would be likely converted to the more stable carbocation **C** through a Single Electron Transfer (SET) event assisted by Co(III). Such carbocation **C** could be further stabilized as the corresponding iminium ion **D**. According to experimental evidences, the latter would be trapped by highly nucleophilic indoles to produce the target product. In contrast, when using less reactive ethers, prior nucleophilic attack of *t*BuOOH would deliver peroxide intermediate **E**,[21] which could eventually react with the *in situ* generated α-oxy radical **F**[14] to produce the corresponding coupling product.

**Scheme 5. Proposed reaction mechanism**




In summary, we have disclosed an unprecedented C($sp^3$)−H functionalization reaction of α-amino carbonyl compounds featuring the use of cost-efficient cobalt catalysis. Both ethers and indoles can be selectively introduced in a variety of glycine derivatives in a straightforward fashion. Importantly, our base-free mild reaction conditions allowed for the full maintenance of the configuration of existing stereocenters. Notably, our method represents an attractive, yet complementary, strategy for peptide modifications which was found to be applicable to the assembly of a vast array of α-

functionalized glycine derivatives of paramount importance in proteomics. We anticipate that our experimental results could lead to acquiring new knowledge in catalyst design, thus opening up new vistas in cobalt-catalyzed C–H functionalizations. Further mechanistic investigations are currently underway in our laboratories.

## ASSOCIATED CONTENT

### Supporting Information

Detailed screening processes, experimental procedures, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interests.

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